Management of Bacteriuria and Urinary Tract Infections in the Older Adult

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KEYWORDS

• Urinary tract infection • Bacteriuria • Older adult • Elderly

KEY POINTS

- Urinary tract infection (UTI) is one of the most frequent bacterial infections diagnosed in the older population and is the most common reason for antibiotic prescriptions in nursing homes.
- A systematic approach to diagnosis with a standard toolkit or algorithm is recommended in patients residing in post-acute and long-term care settings.
- Treatment of UTIs in the older adult is similar to that of the younger adult. Nitrofurantoin and trimethoprim-sulfamethoxazole remain as first-line agents for the treatment of acute simple cystitis for most patients while quinolones have been relegated to second-line given side effects and increasing resistance.
- A shorter duration of therapy has been proven safe and non-inferior in many situations in UTIs.
- Data support the use of vaginal estrogen therapy, methenamine hippurate, and continuous antibiotic prophylaxis in certain populations for the prevention of UTIs in those with recurrent infections. Continuous antibiotic use should only be used if all other measures have failed in carefully selected patients where the benefit of continuous antibiotic may outweigh the risks for resistance and other side effects.

INTRODUCTION

Urinary tract infection (UTI) is one the most common bacterial infections, which in 2007 led to an estimated 10.5 million office visits for UTI symptoms and 2 to 3 million visits to emergency departments.[1] The data from the Nationwide Inpatient Sample showed that in 2011 there were 400000 hospitalizations for UTI with an estimated cost of $2.8 billion. Patients admitted to the hospital had a mean age of 74.7 years and most of them were women (71.4%) with a mean length of stay of 4.24 days.[2]

In patients older than 65, the proportion of admissions with UTI due to isolates with antimicrobial resistance increased from 3.64% in 2009 to 6.88% in 2016 and they were more likely to be discharged to health care facilities compared to routine discharges (Odds ratio [OR]: 1.81. 95% confidence interval [CI], 1.75–1.86).[3]

A 1-day point prevalence survey cross-sectional analysis done in 2017 among nursing home residents within 10 states with an Emerging Infections Program showed that among 15275 nursing home residents, antimicrobial use prevalence was 8.2 per 100 residents (95% CI, 7.8–8.8) with 28.1%

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being used primarily for UTI and 18.2% for prophylaxis, most often for UTI prevention.[4]

Pathophysiology

The increased risk for UTI in the aging population is not completely understood and represents a complex interplay of changes in innate immunity, hormonal changes, chronic inflammation, and impaired mechanisms for the reduction of bacterial burden within the bladder.

Animal models have shed some light on some changes associated with aging. The lysosome is a critical structure for autophagy, cellular and protein turnover, cell signaling, and ion regulation. In the aging urothelium progressive accumulation of large endolysosomes has been seen with impaired luminal degradation and higher potential hydrogen (pH) when compared to younger controls.[5] The aged urothelium has also shown a higher level of reactive oxygen species with a blunted antioxidant response.[6] All these changes contribute to bladder dysfunction. Furthermore, an increased number of quiescent intracellular reservoirs of uropathogenic *Escherichia coli (E. coli)* have been found in the aging epithelium and have been associated with increased recurrence of infection.[6]

Hormonal changes have been associated with disruption of the normal vaginal flora. There is a notable reduction in the vaginal pH of the peri- and postmenopausal women,[7] which has been shown to lead to a loss of lactobacilli colonization and increased isolation of Enterobacterales from vaginal cultures.[8] Vaginal atrophy and uninhibited bladder contraction are also hypothesized to contribute to chronic inflammation in the aging uroepithelium.[9,10]

Microbiology

The prevalence of different pathogens and resistance patterns will largely depend on the population selected. In 2012, a survey of outpatient females from more than 200 institutions in the United States (US) showed that the most frequently identified bacteria were *E. coli* (64.9% of isolates), *Klebsiella pneumoniae* (10.1%), *Proteus mirabilis* (5.0%), *Enterococcus faecalis* (4.1%), and *Pseudomonas aeruginosa* (2.7%).[11]

The National Healthcare Surveillance Network in their 2018 to 2021 report showed that Enterococcus and Pseudomonas species were more common in those with catheter-associated UTIs. The top pathogens for long-term acute care hospitals were *E. coli* (22.8%), Pseudomonas species (22.7%), Klebsiella species (18.6%), Proteus species (8.7%), and *Enterococcus faecalis* (6.4%). For inpatient rehabilitation facilities the most common pathogens were *E. coli* (35.3%), Klebsiella species (17.2%), Pseudomonas species (15.9%), *Enterococcus faecalis* (6.7%), and Proteus species (6.1%).[12]

DIAGNOSTIC APPROACH

Asymptomatic Bacteriuria

The Infectious Diseases Society of America (IDSA) in their 2019 asymptomatic bacteriuria (ASB) guidelines define ASB as the presence of 1 or more species of bacteria growing in the urine at specified quantitative counts ($\geq 10^5$ colony-forming units [CFU]/mL or $\geq 10^8$ CFU/L) regardless of pyuria and in the absence of symptoms consistent with UTI. The guidelines recommend against screening older individuals; these recommendations hold both for healthy independent patients residing in the community and for functionally or cognitively impaired patients residing in long-term care. An exception is made for those planned to undergo invasive urologic procedures in which breakdown of the mucosa is expected.[13]

Symptomatic Urinary Tract Infection

Diagnosing UTI can be complex and varies according to the site of infection in the urinary tract (prostatitis, cystitis, and pyelonephritis), the presence or absence of an indwelling catheter, community versus post-acute and long-term care (PALTC) resident, host characteristics (immunocompromized, spinal cord injury, diabetes, etc.), and severity of infection.

In the cognitively intact older adult, the diagnosis of UTI is similar to that of the younger adult. Clinical diagnosis should be based on localizing signs and symptoms that include dysuria, frequency, urgency, new incontinence, gross hematuria, suprapubic pain, or costovertebral tenderness. However, chronic genitourinary symptoms are common in older adults, which may complicate the diagnosis and this population is also known to have an increased risk of UTI secondary to drug-resistant organisms.[3,14,15] Therefore, urinalysis and urine culture should be obtained in older adults before starting empiric antibiotics to further guide antibiotic treatment.

Making the diagnosis of UTI is more challenging when evaluating cognitively impaired older adults and PALTC residents who may not be able to verbalize their symptoms. AMDA – The Society for Post-Acute and Long-Term Care Medicine recommends adhering to a consensus criteria or validated clinical algorithm for the diagnosis and decision to initiate antibiotics for residents with suspected UTI and performing urinalysis and urine culture only for those who meet clinical criteria.[16]

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Examples of consensus criteria and validated clinical algorithms include Loeb minimum criteria for initiating antibiotics,[17] the Agency for Healthcare Research and Quality toolkit,[18] an international Delphi consensus procedure for the empiric treatment of suspected UTI in frail older adults,[19] and the Improving Outcomes of UTI Management in Long-term Care Project Consensus Guidelines for the diagnosis of Uncomplicated Cystitis in nursing home residents.[20]

Approach to the Patient with Isolated Acute Delirium or Advanced Dementia

For patients with acute delirium and no localizing signs and symptoms of UTI, empirical antibiotic treatment for UTI should be avoided, and clinical observation while assessing other causes should be the primary approach. This is supported by a prospective study that followed patients aged 70 years or elder admitted to a medical unit and screened for delirium while being followed during their hospitalization. The primary outcome assessed the rate of poor functional recovery, which was a composite of death, new long-term care institutionalization, or decreased ability to perform activities of daily life. With a cohort of 343 patients, patients with delirium treated for UTI without urinary symptoms had a worse functional recovery compared to other patients with delirium with an RR of 1.30 (95% CI, 1.14–1.48). Similar results were seen when including patients with bacteriuria and delirium.[21]

Older individuals with advanced dementia represent a diagnostic challenge due to decreased communication capacity, frequent incontinence, and multiple comorbidities. Patients with advanced dementia are frequently misdiagnosed as having UTIs and are overly exposed to antibiotic therapy. In a prospective study from 25 nursing homes in the Boston area, change in mental status was the sole sign or symptom in 35.9% of suspected UTI events and only 16% met the clinical criteria for empirical use of antibiotic therapy. When stratified according to the presence of a urinary catheter, patients without an indwelling catheter were more likely to have mental status change reported on their chart (48.3% vs 13.3%) and less likely to have fever (33.3% vs 19%) and meet clinical criteria for empirical use of antibiotics (12.9% vs 40%). When considering both clinical and microbiological criteria, only 11.4% of suspected events met the criteria for UTI diagnosis but the vast majority received antimicrobial therapy (77.9%).[22]

These studies demonstrate that mental status change including acute delirium in the absence of other signs and symptoms of UTI may indicate alternative etiologies. Careful clinical evaluation and close observation are usually required before pursuing diagnostic workup for UTI in these cases. For PALTC residents with unequivocal delirium, AMDA's infection Advisory Committee consensus statement recommends that a UTI diagnosis should only be considered if there is no other cause identified for these acute, fluctuating symptoms. For those residents with mental status change who do not meet clinical criteria for UTI and do not have any warning signs (such as fevers, rigors, acute delirium, or unstable vital signs), they recommend "active monitoring", which includes observation of vital signs, hydration status, and repeated physical assessments by nursing staff.[16]

TREATMENT

Asymptomatic Bacteriuria

Many prospective studies in the 1980s and 1990s failed to show any clinical benefit in treating ASB. One of these studies performed in Canada evaluated 2 all-male long-term care facilities, which showed that ASB was a frequent finding among their residents ranging between 26% and 47%. Those who showed microbiological failure or relapse after a single dose of antibiotic therapy, they were randomized to either progressively longer courses of antibiotics if persistent failure or relapse or to no treatment at all. Ninety four percent of those in the treatment group had bacteriuria at the study termination versus 100% of those without treatment. There was no statistically significant difference in the number of infections or mortality between the 2 groups and those in the treatment arm showed subsequent bacteriuria with more resistant organisms.[23]

A group that has shown benefits from the treatment of ASB are those patients who will undergo endoscopic urologic procedures in which mucosal trauma is expected. Both the IDSA in their 2019 ASB guidelines and the American Urologic Association in their 2019 Best Practice Statement recommend one or two doses to be given right before the procedure.[13,24] Non-invasive procedures such as urodynamic studies and cystoscopy have not shown benefits from urine culture screening or antibiotic prophylaxis to prevent UTIs or bacteremia.[24,25]

Symptomatic Urinary Tract Infection

The older adult is at risk for adverse drug events and antibiotics should be selected with care and with appropriate monitoring. A good resource is the American Geriatric Society's Beers Criteria for Potentially Inappropriate Medication Use in

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Older Adults, which in its most recent iteration from 2023 lists nitrofurantoin for its potential risk for pulmonary toxicity, hepatotoxicity, and peripheral neuropathy, especially with long-term use and recommends avoiding the medication when creatinine clearance is less than 30 mL per min. It lists trimethoprim-sulfamethoxazole for risk of worsening renal function and hyperkalemia with concurrent use of angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, or angiotensin receptor-neprilysin inhibitor in presence of decreased creatinine clearance. It also recommends against the use of ciprofloxacin with creatinine clearance less than 30 mL per min due to its risk of central nervous system effects like seizure and confusion, as well as the risk of tendon rupture.[26]

Short courses of nitrofurantoin and trimethoprim-sulfamethoxazole remain as first-line treatment for acute simple cystitis for most patients (when there are no contraindications and drug-drug interactions) while quinolones have been relegated as second-line treatment due to their side effects and risk for *C. difficile*. Nitrofurantoin is not recommended for acute pyelonephritis or systemic infection.

Treatment of symptomatic UTI in the older adult does not vary significantly from the recommendations for younger adults. The importance of obtaining an adequate history to evaluate prior antibiotic exposure and review of prior cultures is paramount when deciding to start empiric antibiotic treatment; this was illustrated by the study of Talan and colleagues where patients admitted with a primary diagnosis of UTI were stratified according to infection with Enterobacterales with an extended-spectrum beta-lactamase (ESBL) versus those without ESBL, risk factors included exposure to antibiotics within the last 90 days (75% vs 45.2%), residing in long-term care within 90 days (24.4% vs 7.5%), having a prior history of a ceftriaxone-resistant isolate within the last year (41.6 vs 8.6%), having a prior history of a quinolone-resistant isolate within the last year (41.6 vs 14.7%).[27] Antibiotic choice should be adjusted as needed once culture result becomes available. The choice of empiric antibiotic will also depend on the UTI syndrome being treated (eg, acute simple cystitis vs acute pyelonephritis).

Classification

Classically, UTI has been classified in women as uncomplicated for acute simple cystitis (with infection limited to the bladder) and complicated for pyelonephritis or infection with underlying urologic abnormality (eg, obstructive uropathy).

Historically, in men all UTIs were considered complicated; however, there has been a movement away from this definition as men can also have acute simple cystitis (with infection limited to the bladder), and most recently a new classification for UTIs in men is to divide them into febrile versus non-febrile UTIs.

Uncomplicated or Simple Cystitis in Women

As with many other infectious conditions, there is a growing body of evidence showing that shorter courses of antibiotic therapy are not only effective but safer for patients. A Cochrane review from 2012 showed no significant difference in the number of persistent UTIs within the first 2 weeks of treatment between those who received a short course of antibiotics (3–6 days) compared to long course of treatment (7–14 days) with a RR: 0.85 (95% CI, 0.29–2.47) and no difference between the 2 groups at long-term follow-up with a RR: 0.85 (95% CI, 0.54–1.32).[28]

The 2010 International Clinical Practice Guidelines for the Treatment of Acute Uncomplicated Cystitis and Pyelonephritis in Women, endorsed by the European Society for Microbiology and Infectious Diseases (ESCMID) and the IDSA, gives the following options for the treatment of simple cystitis in women.[29]

- Nitrofurantoin monohydrate or macrocrystals 100 mg twice daily for 5 days.
- Trimethoprim-sulfamethoxazole 160 mg-800 mg twice daily for 3 days.
- Fosfomycin 3 g in a single dose.
- Pivmecillinam 400 mg twice daily for 3 to 7 days. The product is not available in the US.
- Fluoroquinolones for 3 days
- B-lactam agents including amoxicillin-clavulanate, cefaclor, and cefpodoxime for 3 to 7 days

If possible, quinolones should be avoided in UTIs given their risk for side effects including confusion, hypoglycemia, tendon rupture, QT prolongation, and *C difficile* infection.[26] Furthermore, increasing quinolone resistance has also been seen in North America with a systematic review showing that the rate of resistance in *E. coli* isolates from women with uncomplicated infections increased between 2008 and 2017 from 4% to 12%.[30] Similarly, a prospective study from 10 academic emergency departments in the US in patients with pyelonephritis showed that *E coli* isolates in uncomplicated versus complicated pyelonephritis had a quinolone resistance rate of 6.3% (range by site 0.0%– 23.1%) and 19.9% (0.0%–50.0%), respectively.[31]

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Acute Pyelonephritis in Women

The 2010 International Clinical Practice Guidelines for the Treatment of Acute Uncomplicated Cystitis and Pyelonephritis in Women, endorsed by the ESCMID and the IDSA, gives the following options for the treatment of pyelonephritis in women.[29]

- Ciprofloxacin 500 mg twice daily for 7 days.
- Levofloxacin 750 mg once daily for 5 days.
- Trimethoprim-sulfamethoxazole 160 mg-800 mg twice daily for 7 to 14 days (depending on the rapidity of clinical response).
- Oral β-lactam for 10 to 14 days. If this option is used, then a dose of parenteral formulation like ceftriaxone is recommended.

Randomized clinical trials studying shorter durations for trimethoprim-sulfamethoxazole and oral β-lactams are limited. A study comparing 4 systematic reviews with a meta-analysis (which included studies using antibiotics like amoxicillin, cefixime, trimethoprim-sulfamethoxazole, and pivampicillin) showed results favoring a shorter course of antibiotics (≤7 days) when comparing them to longer courses with an RR of clinical failure of 0.70 (95% CI, 0.53–0.94) and no significant difference in the rate of microbiological failure with an RR of 1.06 (95%CI, 0.75–1.49).[32] With these findings, in patients with mild disease and good clinical response to antibiotic therapy, a shorter course of 7 to 10 days of trimethoprim-sulfamethoxazole or oral β-lactam (particularly those who received a dose of parenteral antibiotic) is probably adequate. Another important point to consider when considering the use of ciprofloxacin and levofloxacin for acute pyelonephritis is the increasing prevalence of resistance. In communities where prevalence of *E. coli* fluoroquinolone resistance is more than greater than 10%, a dose of long-acting parenteral antibiotic (such as ceftriaxone) should be administered before starting ciprofloxacin or levofloxacin and culture results should be followed to confirm antibiotic susceptibility. Similarly, when a patient has personal risk factors for having infection with multidrug resistant organisms (eg, recent hospitalization or antibiotic use or infection with multidrug resistant organism), administering a broader spectrum parenteral antibiotic may need to be considered while awaiting the culture results.

Non-febrile Urinary Tract Infection or Acute Simple Cystitis in Men

Men have not been included in the official 2010 guidelines by ESCMID and IDSA, but data support the use of the following.

- Nitrofurantoin monohydrate or macrocrystals 100 mg twice daily for 7 days.
- Trimethoprim-sulfamethoxazole 160 mg-800 mg twice daily for 7 days.
- Fluoroquinolones for 5 to 7 days.
- B-lactam agents like amoxicillin-clavulanate, cefaclor, or cefpodoxime for 7 days.

The use of trimethoprim-sulfamethoxazole and ciprofloxacin for 7 days is supported by a randomized clinical trial done at 2 Veterans Health Administration (VA) Medical Centers where 7 versus 14 days of therapy were compared for men with non-febrile UTI with the primary outcome measuring the proportion of patients reporting resolution of UTI symptoms by day 14 after the completion of the active treatment. With a study population of 272 and a median age of 69, it showed that the primary outcome occurred in 93.1% of the 7-day group versus 90.2% of the 14-day group with a difference of 2.9% (1-sided 97.5% CI of -5.2 to ∞) that was within the 10% non-inferiority margin.[33]

Data supporting shorter duration including additional classes of antibiotics could be seen in a retrospective study in men with non-febrile UTI treated mainly outpatient and selected from 3 specialty clinics and 2 urology private practices that included the use of the following antibiotic classes in descending order of frequency: quinolones, trimethoprim-sulfamethoxazole, nitrofurantoin, and β-lactam that had UTI recurrence as the outcome variable and measured treatment duration as the main exposure (≤7 days vs > 7 days). When controlling for multiple covariates (Charlson comorbidity index, type of antibiotic, diabetes, and age), in their cohort of 573 patients a longer duration of treatment was not associated with decreased rate of recurrence (OR: 1.95, 95% CI, 0.91–4.21).[34]

Febrile Urinary Tract Infection or Complicated Urinary Tract Infectionin Men

- Ciprofloxacin 500 mg twice daily for 7 days.
- Levofloxacin 750 mg once daily for 5 days.
- Trimethoprim-sulfamethoxazole 160 mg-800 mg 7 to 14 days (depending on the rapidity of clinical response).
- Oral β-lactam for 10 to 14 days. If this option is used, then a dose of parenteral formulation like ceftriaxone is recommended.

When selecting empiric antibiotic treatment, same considerations for antibiotic resistance and initial dose of long-acting parenteral agent apply as described earlier for complicated UTI in women. As far as duration is concerned, 2 randomized trials have given somewhat conflicting results. The

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first is a placebo-controlled, double-blind, non-inferiority trial from the Netherlands that enrolled women and men with febrile UTI and randomized them to 7 or 14 days of ciprofloxacin. The primary endpoint was clinical cure rate on post-treatment days 10 to 18 with a non-inferiority margin of 10%. A secondary endpoint also assessed clinical cure at 70 to 84 days post-treatment. With a cohort of 357 patients clinical cure occurred in 90% of the patients treated for 7 days and 95% of those treated for 14 days with a difference of −4.5% (90% CI, −10.7–1.7). Of note, the secondary outcome of clinical cure on long-term follow-up did not show a significant difference with clinical cure in 92% versus 91% with a difference of 1.6% (90% CI, −5.3–8.4).[35]

A multicenter, randomized, placebo-controlled trial from France comparing 7 to 14 days of ofloxacin for febrile UTI in men with a primary outcome of treatment success, which was defined as negative urine culture and absence of fever and subsequent antibiotic treatment between the end of treatment and 6 weeks after day 1. The study enrolled 240 participants and found treatment success in 55.7% of the patients in the 7-day group versus 77.6% in the 14-day group with a risk difference of −21.9% (95% CI, −33.3 to −10.1) showing inferiority. It is important to note that post-treatment culture or "test-of-cure" is not an endpoint that reflects common clinical practice as the recommendations are to avoid sending urinalyses or urine cultures in patients whose clinical symptoms are resolved.[36]

Given that the ideal duration of febrile UTI in men has not been clearly defined, a shorter duration of 7 to 10 days may be used in those with good clinical response who rapidly defervesced, while a longer duration of treatment of 10 to 14 days or more may need to be considered for those with a slow clinical response or additional complicating factors. Furthermore, no randomized clinical trials have been performed to define the duration for acute bacterial prostatitis and expert opinion still recommends a duration of therapy of up to 6 weeks.

PREVENTION

Local Estrogen Therapy

The use of vaginal estrogen therapy has been an underutilized tool for preventing UTIs in patients. In a large survey, up to 80% of postmenopausal women reported at least 1 symptom of vulvovaginal atrophy, 56% had never discussed vaginal symptoms with their health care providers, 20% were told that genitourinary symptoms were a normal part of aging, and only 23% were recommended the use of vaginal estrogen.[37]

Multiple randomized clinical trials have shown a decreased risk of symptomatic UTI in patients treated with vaginal estrogen therapy.[7,8,10,38,39] The largest of these studies from Šimunić and colleagues included 1612 patients with urogenital complaints who were randomized to micronized 17 β-estradiol versus placebo. When comparing UTI rates before treatment versus post-randomization, the estrogen therapy group showed a significant decrease from 23.7% to 6.2% (*P*-value 0.034) during the 12 months of treatment versus no significant difference in the placebo group from 21.1% to 16.4%. Additional benefits were shown in this trial including cystometric examination showing increased capacity and volume at which patient experienced urgency in the estrogen group while also showing less uninhibited detrusor contraction.[10]

Another notable finding was seen in the study of Raz and colleagues in which the cumulative likelihood of remaining UTI-free at 4 months for those receiving estriol cream was 95% versus 30% for those receiving placebo, it also showed that none of the postmenopausal women included in this trial had lactobacilli on vaginal cultures at enrollment but subsequent cultures showed increase colonization by lactobacilli while decreasing colonization by Enterobacterales.[8]

A recent meta-analysis pooled these 5 randomized trials showing an RR of 0.42 (95% CI, 0.30–0.59) for the recurrence of UTI in those patients treated with vaginal estrogen.[40] Given the robust clinical data available, the North American Menopause Society in their 2022 hormone therapy position statement recommends the use of low-dose vaginal estrogen for women with genitourinary syndrome of menopause not relieved with over-the-counter therapies and with no indication for systemic hormone therapy.[41]

Methenamine Hippurate

Methenamine hippurate is hydrolyzed to formaldehyde and ammonia in acidic environments, which has a bactericidal effect by denaturing proteins and nucleic acid. It has been described as an antibiotic-sparring option for those patients with recurrent UTIs. A 2012 Cochrane review could not provide major outcome measures due to the mixed quality of studies with significant underlying heterogeneity; however, subgroup analyses showed that it could be beneficial in preventing UTIs (RR 0.24, 95% CI 0.07–0.89) and ASB (RR 0.56, 95% CI 0.37–0.83) in patients without renal tract abnormalities.[42]

Since the publishing of that Cochrane review in 2012, 2 major randomized clinical trials have been

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published. The first is the ALTAR trial in 2022, which was a pragmatic, open-label, multicenter, randomized, non-inferiority trial based in the United Kingdom comparing methenamine hippurate to low-dose antibiotic therapy with a primary outcome measuring the incidence of symptomatic antibiotic-treated UTI. Of note, this trial included women aged 18 years or elder with recurrent UTIs and excluded those with correctible urinary tract abnormalities and those with neurogenic dysfunction. With 205 participants in the modified-intention-to-treat analysis, the incidence of UTI in the antibiotic group was 0.89 episodes per person-year and 1.38 episodes per person-year in the methenamine group with an absolute difference of 0.49 (90% CI 0.15–0.84), with a defined margin of 1 UTI episode per year; the study confirmed non-inferiority of methenamine when compared to low dose antibiotic prophylaxis.[43]

The second randomized trial was done in the US by Botros and colleagues. This was a single-center, open-label, randomized trial comparing methenamine to trimethoprim in women 18 or older with no urinary tract abnormalities. During the 12 months of follow-up, there was no statistically significant difference in the rate of UTIs, time to UTI, or number of UTIs. Both medications decreased the incidence of UTI from 4 to 1.5 UTI episodes per person-year in the trimethoprim group and from 3.7 to 1.6 episodes per person-year in the methenamine group.[44]

While the ALTAR trial did not specifically target older adults, approximately 60% of the patients were post-or-perimenopausal women. Similarly, the population in the trial by Botros and colleagues had a mean age of 71.9 and 93.4% were postmenopausal. Further research is needed to establish if there is a benefit from using methenamine hippurate in men, patients with urinary tract abnormalities, those with indwelling urinary catheters, and those with neurogenic bladder disorder. For the last group, the SINBA trial in 2006 failed to show improvement in time to recurrence when comparing methenamine to placebo in patients with spinal cord injury, many of whom had suprapubic catheters or had bladder management with clean intermittent self-catheterization.[45]

Continuous Antibiotic Prophylaxis

There has been no randomized clinical trial assessing the efficacy of continuous antibiotic prophylaxis in PALTC population. A randomized, double-blind, non-inferiority trial in the Netherlands comparing low-dose trimethoprim-sulfamethoxazole (single-strength tablet 80/400 mg once daily) to oral lactobacillus for postmenopausal women with recurrent UTIs showed that within their cohort of 252 women, those in the antibiotic group (n = 127), the rate of UTIs in the year before randomization was 7 episodes per year (standard deviation of 4.9) and during the 12 months of treatment the mean number of clinical recurrence was 2.9 (95% CI, 2.3–3.6) with a mean time to first recurrence of 6 months.[46]

A systematic review and meta-analysis published in 2017 assessed the efficacy of long-term antibiotic prophylaxis (duration of treatment in the intervention arms ranging from 6 to 12 months) to prevent recurrent UTIs in older patients (those 65 and older). A total of 3 randomized trials, none of them including men, compared antibiotic prophylaxis to lactobacillus, D-mannose, and vaginal estrogen, respectively. With a pooled cohort of 482 postmenopausal women, the use of antibiotics showed a 24% risk reduction for recurrent UTIs (RR: 0.76; 95% CI, 0.61–0.95) with a number needed to treat of 8.[47]

Continuous antibiotic prophylaxis, while effective, carries many risks including medication side effects in older patients,[26] increased risk for multi-drug resistant organisms,[27] and risk for *C difficile* colitis.[16] In the study performed in the Netherlands comparing trimethoprim-sulfamethoxazole to lactobacillus, after 1 month of antibiotic prophylaxis, the resistance to amoxicillin and trimethoprim-sulfamethoxazole from commensal *E. coli* in urine and feces increased from 20% to 40% to 80% to 95%. After 12 months of antibiotic therapy, all urinary isolates were resistant to trimethoprim-sulfamethoxazole and 38.5% of women had ASB. AMDA – Infection Advisory Committee consensus statement for diagnosis, treatment and prevention of UTI in PALTC residents acknowledge that even though continuous antibiotics may reduce the risk of recurrent, uncomplicated UTIs, the potential harms associated with long-term use, coupled with the prevalence of multidrug-resistant organisms among this patient group argues against long-term antibiotic prophylaxis. Similar risk exists for older patient in community settings too. Therefore, continuous antibiotic use should only be used if all other measures have failed in carefully selected patients where benefit of continuous antibiotic may outweigh the risks for resistance and other side effects. Continuous antibiotic prophylaxis is generally not recommended in patients with indwelling urinary catheters because of even higher risk of resistance.

Therapies with Inconclusive Evidence for the Prevention of Urinary Tract Infection

Probiotic therapy relies on the rationale that loss of vaginal lactobacilli in women has been shown to increase the incidence of gram-negative colonization

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and increased risk for UTI.[8] A 2015 Cochrane review found no reduction in recurrent UTI when comparing probiotic therapy to placebo (RR: 0.82 [95% CI, 0.60–1.12]) and no reduction when comparing probiotic to antibiotic therapy (RR: 1.12 [95% CI, 0.95–1.33]).[48] It is important to mention that the studies included in the Cochrane review had small sample sizes and insufficient methodologic details, which could lead to equivocal findings. Promising results were found in a recent randomized clinical trial from a tertiary care teaching hospital in India with a factorial design that compared the incidence rate of UTI between patients treated with placebo, oral probiotic, vaginal probiotic, and a combination of oral and vaginal probiotic with symptomatic UTI at 4 months reported as 70.4%, 61.3%, 40.9%, and 31.8%, respectively. There was a significant reduction in both the incidence of UTI and time-to-first symptomatic UTI in the vaginal and combination probiotic group when compared to the placebo and oral probiotic group.[49] More robust data are needed to assess the efficacy of probiotics in preventing UTIs.

D-mannose is a sugar that mimics the host's uroepithelial receptor and competitively binds to the uropathogen decreasing bacterial attachment to the mucosa. A 2022 Cochrane review could not perform a meta-analysis given the lack of comparable groups among the different studies.[50] Currently, further research with high-quality randomized clinical trials is needed to support the use of D-mannose.

Cranberry may decrease the adherence of uropathogens to the uroepithelial cells. There have been multiple randomized clinical trials exploring the use of cranberry for decreasing the risk of UTIs. A Cochrane review was recently updated with 26 new studies. Overall, cranberry seems to decrease the risk of UTIs with a RR of 0.70 (95% CI, 0.58–0.84; I^2: 69%); however, when subgroup analyses were performed, the risk in elderly institutionalized men and women showed no benefit with a RR of 0.93 (95% CI, 0.67–1.30; I^2: 9%).[51]

GOALS OF CARE IN THE PATIENT NEAR THE END OF LIFE

A careful balance should be achieved in the care of the older patient near the end of life. Every antibiotic exposure could be complicated by adverse drug events including *C difficile* infection and colonization or infection by multi-drug resistant organism.[27] Additionally, while overly conservative management may feel appropriate in frail patients near the end of life, antibiotic treatment is not always associated with improved outcomes. In a large cohort from 35 nursing homes in the Boston area, those adults aged 65 years or elder with advanced dementia and suspected UTI in whom antibiotics were used (oral, intramuscular, or intravenous), an adjusted Cox proportional hazards regression showed that antibiotic treatment was not associated with mortality.[52] This study shows that overutilization of antibiotic therapy and attributing non-specific symptoms to UTI is not an infrequent occurrence in older patients.

While being near the end of life or being enrolled in hospice is not a contraindication to receiving antibiotic therapy, having a systematic approach for the diagnosis of UTI, including using active monitoring in those with unclear presentation, will help avoid unnecessary use of antimicrobials. Finally, in cases where UTI is suspected, having a conversation regarding the goals of care and explaining the risks and benefits of antibiotic therapy will aid the provider in how to best approach management while honoring the patient's wishes.

CLINICS CARE POINTS

- Screening and treatment for asymptomatic bacteriuria is not recommended unless the patient is planned for a urological procedure in which injury to the mucosa is expected.
- For PALTC residents with mental status change who do not meet clinical criteria for UTI and do not have any warning signs (such as fevers, rigors, acute delirium, or unstable vital signs), active monitoring while investigating alternative causes should be the primary approach.
- Obtaining an adequate history to evaluate prior antibiotic exposure and review prior cultures is paramount when selecting an empiric antibiotic treatment.
- The use of vaginal estrogen is an underutilized tool for the prevention of UTIs in peri and post-menopausal women. Multiple randomized clinical trials have shown a decreased risk of symptomatic UTI with its use.

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